

UCSF

UC San Francisco Previously Published Works

Title

Association of increased upper trunk and decreased leg fat with 2-h glucose in control and HIV-infected persons.

Permalink

<https://escholarship.org/uc/item/3x08x53g>

Journal

Diabetes care, 34(11)

ISSN

0149-5992

Authors

Kosmiski, Lisa A
Scherzer, Rebecca
Heymsfield, Steven B
et al.

Publication Date

2011-11-01

DOI

10.2337/dc11-0616

Peer reviewed

Association of Increased Upper Trunk and Decreased Leg Fat With 2-h Glucose in Control and HIV-Infected Persons

LISA A. KOSMISKI, MD¹
 REBECCA SCHERZER, PHD^{2,3}
 STEVEN B. HEYMSFIELD, MD⁴
 DAVID RIMLAND, MD⁵
 MICHAEL S. SIMBERKOFF, MD⁶
 STEPHEN SIDNEY, MD⁷
 MICHAEL G. SHLIPAK, MD^{2,3}

PETER BACCHETTI, PHD⁸
 MARY L. BIGGS, PHD⁹
 CARL GRUNFELD, MD^{2,3}
 FOR THE STUDY OF FAT REDISTRIBUTION AND
 METABOLIC CHANGE IN HIV INFECTION
 (FRAM)*

OBJECTIVE—Changes in body fat distribution and abnormal glucose metabolism are common in HIV-infected patients. We hypothesized that HIV-infected participants would have a higher prevalence of impaired glucose tolerance (IGT) compared with control subjects.

RESEARCH DESIGN AND METHODS—A total of 491 HIV-infected and 187 control participants from the second examination of the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM) underwent glucose tolerance testing (GTT). Multivariable regression was used to identify factors associated with GTT parameters.

RESULTS—The prevalence of impaired fasting glucose (IFG) (>110 mg/dL) was similar in HIV-infected and control participants (21 vs. 25%, $P = 0.23$). In those without IFG, the prevalence of IGT was slightly higher in HIV-infected participants compared with control subjects (13.1 vs. 8.2%, $P = 0.14$) and in HIV+ participants with lipoatrophy versus without (18.1 vs. 11.5%, $P = 0.084$). Diabetes detected by GTT was rare (HIV subjects 1.3% and control subjects 0%, $P = 0.65$). Mean 2-h glucose levels were 7.6 mg/dL higher in the HIV-infected participants ($P = 0.012$). Increased upper trunk subcutaneous adipose tissue (SAT) and decreased leg SAT were associated with 2-h glucose and IGT in both HIV-infected and control participants. Adjusting for adipose tissue reduced the estimated effects of HIV. Exercise, alcohol use, and current tenofovir use were associated with lower 2-h glucose levels in HIV-infected participants.

CONCLUSIONS—In HIV infection, increased upper trunk SAT and decreased leg SAT are associated with higher 2-h glucose. These body fat characteristics may identify HIV-infected patients with normal fasting glucose but nonetheless at increased risk for diabetes.

Diabetes Care 34:2448–2453, 2011

The estimated prevalence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) in the general U.S. population is 26 and 15%, respectively (1). Approximately 25% of adults

with IFG or IGT progress to diabetes over 3–5 years. However, there are relatively little data regarding the prevalence of IGT in HIV-infected persons. The factors associated with IFG and IGT in the

HIV-infected population have also not been well characterized.

In HIV infection, the prevalence of IFG ranges from 2.2% in Kenyans to 21% in U.S. men (2–5). In women receiving antiretroviral therapy, the prevalence of IGT was 17% compared with 9% of uninfected control subjects (6). In another study, 16% of HIV-infected men receiving antiretroviral therapy had IGT versus 18% of uninfected control participants (3). In healthy control subjects taking protease inhibitors (PIs) and HIV-infected subjects receiving combination antiretroviral therapy, diabetes is more likely to be diagnosed by glucose tolerance testing (GTT) than by fasting glucose (7,8). Peak PI levels acutely inhibit insulin-mediated glucose disposal, which may explain increased abnormalities with GTT compared with fasting glucose (7,8). Increased visceral adipose tissue (VAT) and upper trunk subcutaneous adipose tissue (SAT) were independently associated with insulin resistance in both HIV-infected and control participants in the Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). The prevalence of insulin resistance defined by homeostasis model assessment (HOMA) >4 was 37% in HIV-infected participants and 28% in control subjects ($P = 0.005$) (9). In HIV-infected subjects, age, alcohol use, and male sex were associated with insulin resistance.

During the second FRAM examination, GTT was performed. Because insulin resistance, IFG, and IGT are not equivalent concepts, analysis of the latter parameters can provide insight into glucose metabolism in HIV infection and its relation to demographic factors and regional adiposity.

RESEARCH DESIGN AND METHODS

FRAM was designed to evaluate the prevalence and correlates of changes in fat distribution, insulin resistance, and dyslipidemia in a representative sample of HIV-infected and control participants in the U.S. (10).

Study population

In 1999, the first FRAM examination enrolled 1,183 HIV-infected participants.

From the ¹University of Colorado, Denver, Colorado; the ²Department of Medicine, University of California, San Francisco, California; the ³Veterans Affairs Medical Center, San Francisco, California; the ⁴Pennington Biomedical Research Center, Baton Rouge, Louisiana; the ⁵Division of Infectious Diseases, Veterans Affairs Medical Center, and Emory University School of Medicine, Decatur, Georgia; the ⁶Department of Medicine, Veterans Affairs Medical Center New York Harbor Healthcare System and New York University School of Medicine, New York, New York; the ⁷Division of Research, Kaiser Permanente, Oakland, California; the ⁸Department of Epidemiology and Biostatistics, University of California, San Francisco, California; and the ⁹Department of Biostatistics, University of Washington, Seattle, Washington.

Corresponding author: Carl Grunfeld, carl.grunfeld@ucsf.edu.

Received 30 March 2011 and accepted 9 August 2011.

DOI: 10.2337/dc11-0616. Clinical trial reg. no. NCT00331448, clinicaltrials.gov.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-0616/-/DC1>.

*A complete list of investigators can be found in the Supplementary Data online.

© 2011 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

Control subjects were recruited from two centers participating in the Coronary Artery Risk Development in Young Adults (CARDIA) study (10). CARDIA participants were originally recruited as a sample of healthy white and African American men and women aged 18–30 years from four cities in 1985–1986 for a longitudinal study of cardiovascular risk factors. CARDIA GTT data were obtained at the 2005–2006 examination.

The second FRAM examination was conducted ~5 years later; 824 participants (581 HIV-infected and 241 control subjects) were reevaluated. Both FRAM protocols were approved by local institutional review boards.

GTT

The second FRAM examination included GTT. Participants with known diabetes or taking diabetes medication were to be excluded from GTT. However, GTT was performed in 14 subjects subsequently found to have diabetes by fasting levels during the GTT and in 17 subjects who were taking diabetes medications. Diabetes was defined by a fasting blood glucose level of ≥ 126 mg/dL (7.0 mmol/L) or a reported use of insulin or oral hypoglycemic medication. Two-hour glucose levels from GTT were available in 678 nondiabetic participants (491 HIV-infected and 187 control subjects).

After a 10-h overnight fast, subjects received 75 g glucose orally. Blood samples were collected at 0 and 120 min for measurement of plasma glucose and serum insulin. HIV-infected participants were instructed to take their PI before the GTT. All GTT blood specimens were analyzed by Linco Research (St. Louis, MO), with the exception of 24 samples analyzed by Yellow Springs Instruments (Yellow Springs, OH).

IGT was defined as 2-h glucose > 140 mg/dL, and diabetes was defined as 2-h glucose > 200 mg/dL. Two cut points were considered and compared to define IFG: 100 and 110 mg/dL.

Calibration of glucose values

In HIV-infected participants, GTT was performed on average within 9 days of other FRAM2 measurements. In control participants, GTT was performed at the CARDIA year 20 examination and occurred on average 234 days earlier than FRAM2 measurements. A comparison of GTT fasting glucose with the FRAM2 examination fasting glucose suggested laboratory drift over time in control

participants' fasting glucose measurements. Therefore, we calibrated fasting and 2-h glucose from GTT to fasting glucose from FRAM2 for control participants, as described in the Supplementary Data. Results of calibrated and uncalibrated analyses are also compared in the Supplementary Data.

Magnetic resonance imaging

Regional and total adipose tissue (AT) volumes were quantified by whole-body magnetic resonance imaging (MRI), as described previously (11). A single analyst read all scans at the Obesity Research Center, St. Luke's Roosevelt Hospital (New York, NY). Anatomic sites considered were leg, lower trunk (abdomen and back), upper trunk (chest and back), and arm.

Other measurements

Standardized questionnaires and protocols were used to determine demographic characteristics; height; weight; medical history; risk factors for HIV; physical activity; and alcohol, tobacco, and illicit drug use (10). Research associates interviewed subjects and reviewed medical charts regarding antiretroviral therapy use. AIDS was defined as CD4 lymphocyte count < 200 or history of opportunistic infection (OI) or other AIDS-defining illness.

Hepatitis C virus RNA testing was performed using the Bayer Versant 3.0 branched DNA assay (Bayer AG, Leverkusen, Germany). CD4 lymphocyte count, HIV RNA level in HIV-infected participants, and other blood specimens were analyzed in a single centralized laboratory (Covance, Indianapolis, IN).

Statistical methods

Analyses that compared HIV-infected participants with control subjects included only the 309 HIV-infected participants who were within the age range of 38 to 52 years age range of control subjects. Characteristics were tested for statistical significance using a *t* test for continuous variables and Fisher exact test for categorical variables. The Mann-Whitney *U* test was used for variables that did not have a normal distribution.

We used multivariable linear and logistic regression to evaluate the association of HIV with GTT parameters. We also constructed models in HIV-infected and control participants separately. Outcomes included diabetes by GTT (2-h glucose > 200 mg/dL), IGT, IFG, and 2-h

glucose concentration. Models were constructed in a staged fashion using HIV status, demographics (age, sex, and race), lifestyle factors, and MRI AT depots as predictor variables. We defined lipoatrophy as leg SAT below the 10th percentile of control subjects, with men and women tested separately (12). Age, sex, and race were forced in every model. Linearity was assessed by adding quadratic terms to the models and examining generalized additive models. CIs were determined using the bias-corrected accelerated bootstrap method (11). Candidate lifestyle factors included physical activity (quartiled in men and women separately), smoking, alcohol use, food intake, and illicit drug use.

Because of their skewed distribution, AT depots were \log_2 -transformed in all regression analyses (associations with the outcome are per doubling). Covariates for each model were selected using Bayesian model averaging; predictors with posterior probabilities $> 35\%$ were retained in the model (13). Interactions of HIV status with sex, ethnicity, and age were assessed; none reached statistical significance (all $P > 0.15$). Missing covariate values were imputed using multiple imputation with the Markov chain Monte Carlo method for arbitrary missing data (14).

HIV-related candidate variables included AIDS diagnosis, reported HIV duration, HIV RNA level (\log_{10}), current and nadir CD4 count (\log_2), hepatitis C virus infection RNA, days since last OI, OI status (last 100 days), and risk factors for HIV acquisition. Current use of each antiretroviral drug and class were also evaluated.

Posterior probabilities were calculated using the BMA package for the R statistical computing language (R Development Core Team, Vienna, Austria). Other analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

RESULTS

Subject characteristics

GTT was performed in 491 HIV-infected and 187 control subjects without diabetes, whose characteristics are presented in Table 1. Age-restricted HIV-infected and control participants were of similar age, height, and percentage of Caucasians and African Americans, but the percentage of men was higher in the HIV-infected group by design (70 vs. 55%). BMI and amount of SAT were significantly lower in HIV-infected participants ($P < 0.001$).

Table 1—Demographic and clinical characteristics of HIV-infected and control participants

Parameter	All HIV-infected subjects (n = 491)	Age-restricted subjects*	
		HIV infected (n = 309)	Control (n = 187)
Age (years)	47.0 (41.0–53.0)	45.0 (42.0–49.0)	46.0 (42.0–48.0)
Sex (%)			
Female	140 (29)	92 (30)	85 (45)
Male	348 (71)	216 (70)	102 (55)
Transgendered	3 (1)	1 (1)	0
Ethnicity (%)			
White	242 (49)	148 (48)	110 (59)
African American	185 (38)	119 (39)	77 (41)
Other	64 (13)	42 (14)	0
Height (cm)	172.7 (166.7–179.3)	173.5 (166.4–180.0)	172.2 (164.7–179.4)
Weight (kg)	75.0 (65.2–85.1)	75.0 (65.3–86.1)	82.7 (69.8–93.9)
BMI (kg/m ²)	24.9 (22.1–27.7)	24.9 (22.0–27.8)	27.2 (24.1–31.7)
VAT (kg)	2.5 (1.3–4.1)	2.3 (1.3–3.9)	2.7 (1.5–4.0)
Leg SAT (kg)	3.4 (2.4–5.5)	3.6 (2.4–5.7)	6.0 (4.8–9.0)
Lower trunk SAT (kg)	4.4 (2.6–7.3)	4.5 (2.5–7.6)	7.5 (5.3–10.9)
Upper trunk SAT (kg)	3.4 (2.3–5.2)	3.4 (2.2–5.2)	4.5 (3.3–6.5)
VAT-to-abdominal fat ratio	0.32 (0.20–0.49)	0.30 (0.19–0.48)	0.24 (0.17–0.35)
Fasting glucose (mg/dL)	93.0 (85.0–100.0)	92.0 (85.0–98.0)	92.0 (86.0–99.0)
Insulin (μ U/mL)	15.0 (10.0–22.0)	15.0 (9.0–20.0)	13.0 (9.0–20.0)
HOMA	3.3 (2.1–5.1)	3.3 (2.0–4.9)	2.9 (2.0–4.8)
Current CD4 (cells/ μ L)	421 (267–622)	407 (258–613)	
HIV RNA (1,000/mL)	0.4 (0.4–1.8)	0.4 (0.4–2.4)	

Excludes those with missing 2-h glucose and those with fasting glucose ≥ 126 mg/dL or taking diabetes medication. Continuous data are presented as median (interquartile range). *Age restricted to 38–52 years.

Median VAT was slightly lower in HIV-infected persons (2.3 vs. 2.7 kg, $P = 0.11$), whereas the ratio of VAT to total abdominal AT was higher (0.30 vs. 0.24, $P = 0.0003$). Median fasting glucose, fasting insulin, and HOMA levels were similar between the groups.

Diabetes and IGT in HIV-infected and control subjects

In the full cohort (all enrolled subjects with and without GTT), 9.5% of HIV-infected subjects and 7.1% of control participants ($P = 0.34$) had previously diagnosed diabetes. IFG was common in both groups (HIV participants 21% and control participants 25%, $P = 0.23$).

Among those with GTT performed, the prevalence of diabetes by fasting glucose ≥ 126 mg/dL was low in both HIV-infected and control participants (3.7 vs. 4.1%, $P = 0.84$). These individuals were excluded from further analysis. Diabetes detected by GTT was also rare (Table 2).

IGT in HIV-infected and control participants

IGT was found in 16.8% of HIV-infected participants and in 12.3% of control

participants ($P = 0.17$, Table 2). When subjects with IFG were excluded, results were similar (13.1 and 8.2%). Mean 2-h glucose values were 7.6 mg/dL higher in HIV-infected participants than in control participants ($P = 0.012$) and remained 7.3 mg/dL higher after demographic adjustment. Further adjustment for AT volume attenuated the difference to 4.3 mg/dL ($P = 0.20$). Likewise, the odds ratio for IGT in HIV-infected versus control subjects was attenuated after adjustment for AT. There were no statistically significant differences in the prevalence of IGT between HIV-infected and uninfected smokers or nonsmokers (Supplementary Table 1).

Factors associated with 2-h glucose and IGT in HIV-infected and control subjects

Higher upper trunk SAT and lower leg SAT were independently associated with higher 2-h glucose values in both HIV-infected and control participants in multivariable analysis (Table 3). Total trunk SAT and lower trunk SAT were also associated with increased 2-h glucose values, but the best model fit was with upper trunk SAT. In multivariable analysis, the

VAT-to-abdominal fat ratio showed little association with 2-h glucose values in either group (Table 3) and resulted in little change in the associations of upper trunk and leg SAT with 2-h values. Greater alcohol use and physical activity (highest quartile) were associated with lower 2-h glucose values in HIV-infected participants, but showed little association in control subjects.

Current tenofovir use was associated with 7.4 mg/dL lower 2-h glucose in the HIV-infected group (95% CI -14.1 to -0.59 ; $P = 0.033$); the tenofovir association was not related to differences in AT. Associations of other antiretroviral medications with 2-h glucose were weaker and did not reach statistical significance. For example, current PI use was associated with 3.7 mg/dL higher glucose (95% CI -3.1 to 10.5 ; $P = 0.28$). Likewise, stavudine and zidovudine were weakly associated with higher 2-h glucose, and their associations did not reach statistical significance. Other HIV-related factors, including CD4 count and HIV RNA levels, showed generally weak associations with 2-h glucose and IGT, and did not enter the multivariable models.

Similar associations of upper trunk SAT, leg SAT, and other factors were seen when IGT was modeled as a dichotomous outcome (Table 4). IGT was more prevalent in HIV-infected participants with lipodystrophy compared with those without, both overall (23.3 vs. 14.4%, $P = 0.015$) and in those without IFG (18.1 vs. 11.5%, $P = 0.084$). Smoking showed little association with IGT in either group and did not attenuate the associations of lifestyle and body composition with IGT.

CONCLUSIONS—Among participants without previously diagnosed diabetes, GTT in the FRAM cohort found higher 2-h glucose levels in HIV-infected participants compared with control participants. The prevalence of IGT was slightly higher in HIV-infected participants, although the difference did not reach statistical significance. The prevalence of IGT in those without IFG was also slightly higher in HIV-infected participants. Undiagnosed IGT may therefore be more common in the HIV-infected population.

HIV-infected participants had lower BMI than control participants. Nevertheless, regional body fat significantly contributed to group differences in 2-h glucose and IGT. Both increased upper trunk SAT and decreased leg SAT were associated with higher 2-h glucose and IGT. Because IGT is

Table 2—Analysis of GTT parameters by HIV status

Measure	Age-restricted subjects*			P value
	HIV infected (n = 309)	Control (n = 187)	All (n = 496)	
Diabetes (2 h >200 mg/dL), % (n)	1.3 (4/309)	0 (0/187)		0.65
OR for HIV+ vs. control subjects (95% CI)			NA	
IGT (2 h >140 mg/dL), % (n)	16.8 (52/309)	12.3 (23/187)		
OR for HIV+ vs. control subjects (95% CI)				
Unadjusted			1.44 (0.85–2.45)	0.17
Adjusted for demographics			1.32 (0.76–2.30)	0.33
Final model with AT**			0.84 (0.44–1.62)	0.61
IGT (2 h >140 mg/dL) in those without IFG100, % (n)‡	13.1 (33/252)	8.2 (12/146)		
OR for HIV+ vs. control subjects (95% CI)				
Unadjusted			1.68 (0.84–3.37)	0.14
Adjusted for demographics			1.61 (0.78–3.33)	0.20
Final model with AT**			1.14 (0.50–2.59)	0.76
2-h glucose (mg/dL)				
Median (IQR)	105.0 (83–128)	96.3 (78.3–121.3)		
Mean ± SD	108.9 ± 35.9	101.3 ± 32.7		
Mean difference HIV+ vs. control subjects (95% CI)				
Unadjusted			7.6 (1.7–13.6)	0.012
Adjusted for demographics			7.3 (1.0–13.5)	0.023
Final model with AT**			4.3 (–2.3 to 10.8)	0.20

P values in boldface denote statistical significance at $P < 0.05$. Those with fasting glucose ≥ 126 mg/dL or taking diabetes medication are excluded. IQR, interquartile range; OR, odds ratio. *All analyses are age restricted to 38–52 years. **Final model adjusts for demographics and AT. ‡IFG100 is defined as fasting glucose > 100 mg/dL.

associated with progression to diabetes, future risk of diabetes may be elevated in HIV-infected persons who lose leg SAT, which is often profound (11) and unlikely

to recover with time (15). Loss of leg SAT is readily recognizable by most clinicians, and individuals with this finding may benefit from GTT even if fasting glucose is normal.

We found a relatively small 7–8 mg/dL increase in 2-h glucose in HIV-infected persons. To place this in perspective, the Cardiovascular Health

Table 3—Multivariable linear regression of factors associated with 2-h glucose (mg/dL) in all HIV-infected and control participants

	HIV+ subjects (n = 491)			Control subjects (n = 187)		
	Estimate	95% CI	P value	Estimate	95% CI	P value
Female vs. male	–3.8	(–13.7 to 6.2)	0.46	12.5	(–2.6 to 27.5)	0.10
African American vs. Caucasian	–2.4	(–9.9 to 5.1)	0.53	4.1	(–5.0 to 13.1)	0.37
Other vs. Caucasian	0.75	(–9.6 to 11.1)	0.89			
Age (per decade)	9.0	(4.4–13.5)	0.0001	2.2	(–10.3 to 14.8)	0.72
Drinks						
<1 vs. none	–2.0	(–10.6 to 6.6)	0.65	–1.8	(–17.2 to 13.6)	0.82
1–7 vs. none	–7.5	(–15.2 to 0.27)	0.059	–0.81	(–15.7 to 14.1)	0.92
>7 vs. none	–17.6	(–28.6 to –6.5)	0.0019	–0.10	(–19.8 to 19.6)	0.99
Physical activity						
2nd vs. 1st quartile	8.4	(–1.11 to 17.8)	0.084	3.2	(–11.6 to 18.0)	0.67
3rd vs. 1st quartile	0.64	(–9.1 to 10.3)	0.90	9.6	(–3.3 to 22.5)	0.14
4th vs. 1st quartile	–10.5	(–18.4 to –2.7)	0.0088	5.4	(–8.4 to 19.3)	0.44
Upper trunk SAT (doubling)	13.8	(8.9–18.6)	<0.0001	20.4	(11.1–29.7)	<0.0001
Leg SAT (doubling)	–10.0	(–16.3 to –3.7)	0.0017	–16.4	(–30.4 to –2.5)	0.020
Tenofovir use	–7.4	(–14.1 to –0.59)	0.033			
Pertinent negatives						
VAT (doubling)	2.1	(–2.2 to 6.4)	0.34	5.8	(–4.4 to 15.9)	0.25
VAT-to-abdominal fat ratio (doubling)	3.4	(–2.0 to 8.8)	0.22	–5.5	(–26.1 to 15.1)	0.59
Current vs. never smoking	2.0	(–5.8 to 9.8)	0.61	–1.9	(–19.3 to 15.4)	0.83
Past vs. never smoking	–1.3	(–9.9 to 7.3)	0.77	–2.7	(–15.8 to 10.3)	0.68

P values in boldface denote statistical significance at $P < 0.05$. Unselected factors are in italics; values shown are those that would result if the factors were added back to the model individually. Those with fasting glucose ≥ 126 mg/dL or taking diabetes medication are excluded. Separate models were constructed for HIV-infected and control participants.

Table 4—Multivariable logistic regression of factors associated with IGT in all HIV-infected and control participants

	HIV+ subjects (n = 491)			Control subjects (n = 187)		
	OR	95% CI	P value	OR	95% CI	P value
Female vs. male	0.61	(0.28–1.32)	0.21	3.39	(0.87–13.12)	0.077
African American vs. white	1.04	(0.58–1.87)	0.90	1.54	(0.60–3.97)	0.37
Other vs. white	1.27	(0.58–2.77)	0.55			
Age (per decade)	1.73	(1.28–2.35)	0.0003	0.59	(0.16–2.19)	0.43
Drinks						
<1 vs. none	0.88	(0.47–1.65)	0.69	0.26	(0.06–1.06)	0.060
1–7 vs. none	0.69	(0.37–1.28)	0.24	0.27	(0.07–1.03)	0.056
>7 vs. none	0.37	(0.15–0.90)	0.028	0.83	(0.20–3.40)	0.80
Physical activity						
2nd vs. 1st quartile	1.51	(0.82–2.78)	0.18	2.08	(0.50–8.77)	0.32
3rd vs. 1st quartile	1.57	(0.82–3.03)	0.17	1.60	(0.43–5.91)	0.48
4th vs. 1st quartile	0.41	(0.18–0.97)	0.042	1.17	(0.25–5.45)	0.84
Upper trunk SAT (doubling)	2.11	(1.43–3.12)	0.0002	3.56	(1.41–8.97)	0.0069
Leg SAT (doubling)	0.57	(0.36–0.91)	0.018	0.17	(0.05–0.62)	0.0069
Pertinent negatives						
VAT (doubling)	1.16	(0.85–1.58)	0.35	2.85	(0.90–9.01)	0.070
VAT-to-abdominal fat ratio (doubling)	1.19	(0.78–1.84)	0.42	3.41	(0.62–18.7)	0.14
Current vs. never smoking	1.07	(0.61–1.91)	0.81	1.43	(0.37–5.54)	0.61
Past vs. never smoking	0.65	(0.34–1.23)	0.19	1.57	(0.44–5.56)	0.49
Tenofovir use	0.75	(0.45–1.23)	0.25			

P values in boldface denote statistical significance at $P < 0.05$. IGT is defined as 2-h glucose >140 mg/dL. Unselected factors (pertinent negatives) are in italics; values shown are those that would result if the factors were added back to the model individually. Those with fasting glucose ≥ 126 mg/dL or taking diabetes medication are excluded. Separate models were constructed for HIV-infected and control participants. OR, odds ratio.

Study found a 2% increased risk of incident cardiovascular disease event for every 10 mg/dL increase in 2-h glucose, plus an additional 29% increase in risk for those with 2-h values >154 mg/dL, in demographic-adjusted analysis (16). Therefore, increased 2-h oral glucose tolerance test values may contribute to the increased cardiovascular disease risk in HIV-infected persons.

The association of regional adiposity with insulin resistance and diabetes has been studied in the general population. VAT is associated with insulin resistance and widely regarded as the regional depot most associated with metabolic disturbances. However, other studies have found important associations between SAT depots and insulin resistance (17–20). For example, in 39 middle-aged men, the sum of truncal skinfold thicknesses was significantly and negatively associated with insulin sensitivity, even after adjusting for total AT (17). In addition, both abdominal and truncal SAT had stronger correlations with insulin sensitivity than did VAT (17). Likewise, in obese women, truncal SAT was independently associated with insulin resistance after

adjustment for total AT and VAT (18). In 783 young men, abdominal SAT, but not VAT, independently predicted higher insulin resistance (19). These studies did not specifically measure upper trunk SAT, so it is of interest that the inclusion of this depot in our multivariable models was adequate to explain the association of increased truncal AT with abnormal glucose metabolism. VAT showed little independent association with 2-h glucose or IGT in our models after controlling for upper trunk and leg SAT.

Gluteofemoral (leg) SAT has been directly associated with increased insulin sensitivity in the general population, in contrast with SAT in the abdomen and trunk. In the Hoorn Study, increased leg fat was associated with lower HOMA insulin resistance in both men and women (21). In the Health ABC study, increased leg fat was independently associated with more favorable fasting and postload glucose levels in men, with weaker results in women (20).

Subcutaneous fat is the major source of the adipokines, leptin and adiponectin, which improve insulin sensitivity. In HIV-infected patients with significant

lipoatrophy, the normal relationship between SAT depots and adiponectin levels is lost or even reversed (12). In other words, in HIV lipoatrophy, depleted AT is associated with lower rather than higher levels of adiponectin, contrary to the general population. Low adiponectin and leptin levels may contribute to insulin resistance in HIV-associated lipoatrophy.

Finally, current tenofovir use was associated with lower 2-h glucose, consistent with a report that patients who switched from stavudine regimens to tenofovir had an average 4 mg/dL decrease in glucose over 48 weeks (22). Both stavudine and zidovudine were associated with higher postprandial glucose in our study, but their associations did not reach statistical significance. We also found that tenofovir's protective effect was not mediated through differences in total or regional adiposity. The increasing use of tenofovir, rather than the earlier thymidine-analog nucleoside reverse transcriptase inhibitors, especially in those with lipoatrophy, may therefore be an ameliorating factor to reduce the risk of diabetes in HIV-infected persons.

PI use showed little association with glucose levels, in contrast with previous studies (23). To date, only indinavir use has been associated with elevated fasting glucose in healthy volunteers (8). By the time of the FRAM2 examination, few participants were taking indinavir. Furthermore, although insulin resistance contributes to increased fasting glucose, defects in insulin secretion are more important. Current-generation PIs may not affect insulin secretion (24).

The primary limitations of this study are its cross-sectional design and the use of calibrated glucose values for the control subjects. However, analysis of factors associated with 2-h glucose is not affected by the calibration, because the analyses were done separately in HIV-infected and control participants. GTT was not performed at the first FRAM examination, so changes in glucose tolerance over time could not be studied. Also, we were unable to measure liver fat, which has been strongly associated with increased risk of IFG, IGT, and insulin resistance, independently of visceral fat (25). Strengths of this study include the large population-based HIV cohort and the use of a nationally representative control group. Finally, the use of MRI strengthens the analysis of regional adiposity and its relationship to GTT parameters.

In conclusion, our study suggests that HIV infection is associated with higher 2-h glucose on GTT and a somewhat higher prevalence of IGT. This increase may be driven by differences in body fat. The natural history of this prediabetic state in HIV infection and its association with cardiovascular disease are unknown and need further study. Our data support a role for greater upper trunk SAT and lower leg SAT in disturbed glucose metabolism in both HIV-infected and control subjects. Future studies should address physiologic mechanisms by which upper trunk SAT is metabolically deleterious and leg SAT is protective.

Acknowledgments—This study was supported by National Institutes of Health (NIH) grants R01-DK-57508, HL-74814, HL-53359, K23-AI-66943, and UL1-RR-024131; NIH General Clinical Research Center grants M01-RR-00036, RR-00051, RR-00052, RR-00054, RR-00083, RR-00636, and RR-00865; the Albert L. and Janet A. Schultz Supporting Foundation; and resources and use of facilities of the Veterans Affairs Medical Centers of Atlanta, District of Columbia, New York, and San Francisco.

The funder played no role in the conduct of the study, collection of data, management of the study, analysis of data, interpretation of data, or preparation of the manuscript. A representative of the funding agent participated in planning the protocol.

C.G. has received prior research funding and honorarium from Merck, Bristol-Myers Squibb, Abbott, Serono, and Theratechnologies. No other potential conflicts of interest relevant to this article were reported.

L.A.K., R.S., S.B.H., D.R., M.S.S., S.S., M.G.S., P.B., M.L.B., and C.G. played a role in editing the manuscript. L.A.K., R.S., and C.G. wrote the manuscript. R.S., M.G.S., P.B., and C.G. were responsible for the design of the FRAM study. R.S., P.B., and M.L.B. were responsible for the biostatistical analyses. C.G. designed the analysis, wrote the grant, and obtained the funding.

Parts of this study were presented in abstract form at the 13th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV, Rome, Italy, 14–16 July 2011.

References

- Davidson MB, Genuth S, Fagan TF, Palangio MA. American Diabetes Association Consensus Statement on IFG and IGT. *Clinical Insights in Diabetes* 2007;2–3
- Manuthu EM, Joshi MD, Lule GN, Karari E. Prevalence of dyslipidemia and dysglycaemia in HIV infected patients. *East Afr Med J* 2008;85:10–17
- Howard AA, Floris-Moore M, Lo Y, Arnsten JH, Fleischer N, Klein RS. Abnormal glucose metabolism among older men with or at risk of HIV infection. *HIV Med* 2006;7:389–396
- Mutimura E, Stewart A, Rheeder P, Crowther NJ. Metabolic function and the prevalence of lipodystrophy in a population of HIV-infected African subjects receiving highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* 2007;46:451–455
- Jericó C, Knobel H, Montero M, et al. Metabolic syndrome among HIV-infected patients: prevalence, characteristics, and related factors. *Diabetes Care* 2005;28:132–137
- Howard AA, Floris-Moore M, Arnsten JH, et al. Disorders of glucose metabolism among HIV-infected women. *Clin Infect Dis* 2005;40:1492–1499
- Behrens G, Dejam A, Schmidt H, et al. Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. *AIDS* 1999;13:F63–F70
- Noor MA, Lo JC, Mulligan K, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. *AIDS* 2001;15:F11–F18
- Grunfeld C, Rimland D, Gibert CL, et al. Association of upper trunk and visceral adipose tissue volume with insulin resistance in control and HIV-infected subjects in the FRAM study. *J Acquir Immune Defic Syndr* 2007;46:283–290
- Tien PC, Benson C, Zolopa AR, Sidney S, Osmond D, Grunfeld C. The study of fat redistribution and metabolic change in HIV infection (FRAM): methods, design, and sample characteristics. *Am J Epidemiol* 2006;163:860–869
- Bacchetti P, Gripshover B, Grunfeld C, et al. Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Fat distribution in men with HIV infection. *J Acquir Immune Defic Syndr* 2005;40:121–131
- Kosmiski LA, Bacchetti P, Kotler DP, et al. Relationship of fat distribution with adipokines in human immunodeficiency virus infection. *J Clin Endocrinol Metab* 2008;93:216–224
- Hoeting JA, Madigan D, Raftery AE, Volinsky CT. Bayesian model averaging: a tutorial. *Stat Sci* 1999;14:382–401
- Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res* 1999;8:3–15
- Grunfeld C, Saag M, Cofrancesco J Jr, et al. Study of Fat Redistribution and Metabolic Change in HIV Infection (FRAM). Regional adipose tissue measured by MRI over 5 years in HIV-infected and control participants indicates persistence of HIV-associated lipoatrophy. *AIDS* 2010;24:1717–1726
- Smith NL, Barzilay JI, Shaffer D, et al. Fasting and 2-hour postchallenge serum glucose measures and risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study. *Arch Intern Med* 2002;162:209–216
- Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. *J Clin Invest* 1995;96:88–98
- Marcus MA, Murphy L, Pi-Sunyer FX, Albu JB. Insulin sensitivity and serum triglyceride level in obese white and black women: relationship to visceral and truncal subcutaneous fat. *Metabolism* 1999;48:194–199
- Frederiksen L, Nielsen TL, Wraae K, et al. Subcutaneous rather than visceral adipose tissue is associated with adiponectin levels and insulin resistance in young men. *J Clin Endocrinol Metab* 2009;94:4010–4015
- Snijder MB, Visser M, Dekker JM, et al. Health ABC Study. Low subcutaneous thigh fat is a risk factor for unfavourable glucose and lipid levels, independently of high abdominal fat. *The Health ABC Study. Diabetologia* 2005;48:301–308
- Snijder MB, Dekker JM, Visser M, et al. Hoorn study. Trunk fat and leg fat have independent and opposite associations with fasting and postload glucose levels: the Hoorn study. *Diabetes Care* 2004;27:372–377
- Gerschenson M, Kim C, Berzins B, et al. Mitochondrial function, morphology and metabolic parameters improve after switching from stavudine to a tenofovir-containing regimen. *J Antimicrob Chemother* 2009;63:1244–1250
- Brown TT, Cole SR, Li X, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med* 2005;165:1179–1184
- Pao VY, Lee GA, Taylor S, et al. The protease inhibitor combination lopinavir/ritonavir does not decrease insulin secretion in healthy, HIV-seronegative volunteers. *AIDS* 2010;24:265–270
- Spiliotes EK, Massaro JM, Hoffmann U, et al. Fatty liver is associated with dyslipidemia and dysglycemia independent of visceral fat: the Framingham Heart Study. *Hepatology* 2010;51:1979–1987